DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

P950008

Date SEP 25 1997

From

Director, Office of Device Evaluation (HFZ-400)
Center for Devices and Radiological Health (CDRH)

Subject

Premarket Approval of Richard-James, Inc.'s SILIKON 1000 (purified polydimethylsiloxane) - ACTION

To

The Director, CDRH
ORA ____

ISSUE. Publication of a notice announcing approval of the subject PMA.

FACTS. Tab A contains a FEDERAL REGISTER notice announcing:

(1)a premarket approval order for the above referenced medical device (Tab B); and

(2)the availability of a summary of safety and effectiveness data for the device (Tab C).

RECOMMENDATION. I recommend that the notice be signed and published.

Susan Alpert, Ph.D., M.D.

Attachments
Tab A - Notice
Tab B - Order
Tab C - S & E Summary

DECISION

Approved ___ Disapproved ___ Date _____

Prepared by Deborah Falls, CDRH, HFZ-460, September 2, 1997, (301) 594-2205.

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DRAFT

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[DOCKET NO. _____]

Richard-James, Inc.; Premarket Approval of SILIKON 1000

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing its approval of the application submitted by Richard-James, Inc., Peabody, MA, for premarket approval, under the Federal Food, Drug, and Cosmetic Act (the act), SILIKON 1000. After reviewing the recommendation of the Ophthalmic Devices Panel, FDA's Center for Devices and Radiological Health (CDRH) notified the applicant, by letter of September 25, 1997 of the approval of the application.

DATES: Petitions for administrative review by (insert date 30 days after date of publication in the FEDERAL REGISTER).

ADDRESSES: Written requests for copies of the summary of safety and effectiveness data and petitions for administrative review to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

James F. Saviola,
Center for Devices and Radiological Health (HFZ-460),
Food and Drug Administration,
9200 Corporate Blvd.,
Rockville, MD 20850,
301-594-2018.

SUPPLEMENTARY INFORMATION: On February 22, 1995, Richard-James, Inc., Peabody, MA, submitted to CDRH an application for premarket approval of SILIKON 1000. The device is an intraocular fluid and is indicated for use as a prolonged retinal tamponade in selected cases of complicated retinal detachments where other interventions are not appropriate for patient management. Complicated retinal detachments or recurrent retinal detachments occur most commonly in eyes with proliferative vitreoretinopathy (PVR), proliferative diabetic retinopathy (PDR), cytomegalovirus (CMV) retinitis, giant tears, and following perforating injuries. SILIKON 1000 is also indicated for primary use in detachments due to Acquired Immune Deficiency Syndrome (AIDS) related CMV retinitis and other viral infections affecting the retina.

On January 13, 1997 the Ophthalmic Devices Panel of the Medical Devices Advisory Committee, an FDA advisory committee, reviewed and recommended approval of the application. On September 25, 1997, CDRH approved the application by a letter to the applicant from the Director of the Office of Device Evaluation, CDRH.

A summary of the safety and effectiveness data on which CDRH based its approval is on file in the Dockets Management Branch (address above) and is available from that office upon written request. Requests should be identified with the name of the device and the docket number found in brackets in the heading of this document.

Opportunity for Administrative Review

Section 515(d)(3) of the act, (21 U.S.C. 360e(d)(3)) authorizes any interested person to petition, under section 515(g) of the act, for administrative review of CDRH's decision to approve this application. A petitioner may request either a formal hearing under 21 CFR part 12 of FDA's administrative practices and procedures regulations or a review of the application and CDRH's action by an independent advisory committee of experts. A petition is to be in the form of a petition for reconsideration under 21 CFR 10.33(b)). A petitioner shall identify the form of review requested (hearing or independent advisory committee) and shall submit with the petition supporting data and information showing that there is a genuine and substantial issue of material fact for resolution through administrative review. After reviewing the petition, FDA will decide whether to grant or deny the petition and will publish a notice of its decision in the FEDERAL REGISTER. If FDA grants the petition, the notice will state the issue to be reviewed, the form of the review to be used, the persons who may participate in the review, the time and place where the review will occur, and other details.

Petitioners may, at any time on or before (insert date 30 days after date of publication in the FEDERAL REGISTER), file with the Dockets Management Branch (address above) two copies of each petition and supporting data and information, identified with the name of the device and the docket number found in brackets in the heading of this document. Received petitions may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 515(d), 520(h) (21 U.S.C. 360e(d), 360j(h))) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10) and redelegated to the Director, Center for Devices and Radiological Health (21 CFR 5.53).

Dated:_____.

_____

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

Mr. Wayne Richard
President and CEO
Richard-James, Inc.
Centennial Park
2 Centennial Drive
Peabody, MA 01960

SEP 25 1997

Re: P950008
SILIKON 1000 - Silicone Oil
Filed: February 22, 1995
Amended: March 10, July 25, and July 21, August 18 and 29, and November 9, 16 and 30, 1995; January 11, 16 and 24, April 30, May 10, August 2 and 14, and November 7, 18, 26, 27 and 29, 1996; and January 10 and 13, February 3, July 10, August 1 and 15, and September 24, 1997

Dear Mr. Richard:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the SILIKON 1000. This device is indicated for use as a prolonged retinal tamponade in selected cases of complicated retinal detachments where other interventions are not appropriate for patient management. Complicated retinal detachments or recurrent retinal detachments occur most commonly in eyes with proliferative vitreoretinopathy (PVR), proliferative diabetic retinopathy (PDR), cytomegalovirus (CMV) retinitis, giant tears, and following perforating injuries. SILIKON 1000 is also indicated for primary use in detachments due to Acquired Immune Deficiency Syndrome (AIDS) related CMV retinitis and other viral infections affecting the retina. We are pleased to inform you that the PMA is approved subject to the conditions described below and in the "Conditions of Approval" (enclosed). You may begin commercial distribution of the device upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Expiration dating for this device has been established and approved at 10 months. This is to advise you that the protocol you used to establish this expiration dating is considered an approved protocol for the purpose of extending the expiration dating as provided by 21 CFR 814.39(a)(8).

CDRH will publish a notice of its decision to approve your PMA in the FEDERAL REGISTER. The notice will state that a summary of the safety and effectiveness data upon which the approval is based is available to the public upon request. Within 30 days of publication of the notice of approval in the FEDERAL REGISTER, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the Federal Food, Drug, and Cosmetic Act (the act).

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Ms. Deborah Falls at (301) 594-2205.

Sincerely yours,

Susan Alpert, Ph.D., M.D.
Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure

CONDITIONS OF APPROVAL

APPROVED LABELING. As soon as possible, and before commercial distribution of your device, submit three copies of an amendment to this PMA submission with copies of all approved labeling in final printed form to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration (FDA), 9200 Corporate Blvd., Rockville, Maryland 20850.

ADVERTISEMENT. No advertisement or other descriptive printed material issued by the applicant or private label distributor with respect to this device shall recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the act under the authority of section 515(d)(1)(B)(ii) of the act, all advertisements and other descriptive printed material issued by the applicant or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects and contraindications.

PREMARKET APPROVAL APPLICATION (PMA) SUPPLEMENT. Before making any change affecting the safety or effectiveness of the device, submit a PMA supplement for review and approval by FDA unless the change is of a type for which a "Special PMA Supplement-Changes Being Effected" is permitted under 21 CFR 814.39(d) or an alternate submission is permitted in accordance with 21 CFR 814.39(e). A PMA supplement or alternate submission shall comply with applicable requirements under 21 CFR 814.39 of the final rule for Premarket Approval of Medical Devices.

All situations which require a PMA supplement cannot be briefly summarized, please consult the PMA regulation for further guidance. The guidance provided below is only for several key instances.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification.

A PMA supplement must be submitted if the device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

A "Special PMA Supplement - Changes Being Effected" is limited to the labeling, quality control and manufacturing process changes specified under 21 CFR 814.39(d)(2). It allows for the addition of, but not the replacement of previously approved, quality control specifications and test methods. These changes may be implemented before FDA approval upon acknowledgment by FDA that the submission is being processed as a "Special PMA Supplement - Changes Being Effected." This acknowledgment is in addition to that issued by the PMA Document Mail Center for all PMA supplements submitted. This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of a PMA supplement before implementation of the change and include the use of a 30-day PMA supplement or annual postapproval report. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence with the applicant that the alternate submission is permitted for the change. Before such can occur, FDA and the PMA applicant(s) involved must agree upon any needed testing protocol, test results, reporting format, information to be reported, and the alternate submission to be used.

POSTAPPROVAL REPORTS. Continued approval of this PMA is contingent upon the submission of postapproval reports required under 21 CFR 814.84 at intervals of 1 year from the date of approval of the original PMA. Postapproval reports for supplements approved under the original PMA, if applicable, are to be included in the next and subsequent annual reports for the original PMA unless specified otherwise in the approval order for the PMA supplement. Two copies identified as "Annual Report" and bearing the applicable PMA reference number are to be submitted to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. The postapproval report shall indicate the beginning and ending date of the period covered by the report and shall include the following information required by 21 CFR 814.84:

(1) Identification of changes described in 21 CFR 814.39(a) and changes required to be reported to FDA under 21 CFR 814.39(b).

(2) Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant:

(a) unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and

(b) reports in the scientific literature concerning the device.

If, after reviewing the bibliography and summary, FDA concludes that agency review of one or more of the above reports is required, the applicant shall submit two copies of each identified report when so notified by FDA.

ADVERSE REACTION AND DEVICE DEFECT REPORTING. As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850 within 10 days after the applicant receives or has knowledge of information concerning:

(1) A mixup of the device or its labeling with another article.

(2) Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and

(a) has not been addressed by the device's labeling or

(b) has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.

(3) Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the applicant. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Postapproval Reports" above unless specified otherwise in the conditions of approval to this PMA. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

REPORTING UNDER THE MEDICAL DEVICE REPORTING (MDR) REGULATION. The Medical Device Reporting (MDR) Regulation became effective on December 13, 1984, and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to FDA whenever they receive or otherwise became aware of information that reasonably suggests that one of its marketed devices

(1) may have caused or contributed to a death or serious injury or

(2) has malfunctioned and that the device or any other device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for this PMA, you shall submit the appropriate reports required by the MDR Regulation and identified with the PMA reference number to the following office:

Division of Surveillance Systems (HFZ-531)
Center for Devices and Radiological Health
Food and Drug Administration
1350 Piccard Drive, Room 240
Rockville, Maryland 20850
Telephone (301) 594-2735

Events included in periodic reports to the PMA that have also been reported under the MDR Regulation must be so identified in the periodic report to the PMA to prevent duplicative entry into FDA information systems.

Copies of the MDR Regulation and an FDA publication entitled, "An Overview of the Medical Device Reporting Regulation," are available by written request to the address below or by telephoning 1-800-638-2041.

Division of Small Manufacturers Assistance (HFZ-220)
Center for Devices and Radiological Health
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

SUMMARY OF SAFETY AND EFFECTIVENESS

I. General Information

A. Device Generic Name: purified polydimethylsiloxane (ProCode LWL - Intraocular Fluid)

B. Device Trade Name: SILIKON 1000 (purified polydimethylsiloxane)

C. Applicant's Name and Address:

Richard-James, Inc.
2 Centennial Drive
Peabody, MA 01960

D. Investigational Device Exemptions (IDE) Number:, G900075

E. Date of Panel Recommendation: January 13, 1997

F. Premarket Approval Application (PMA): P950008
Date Filed: February 22, 1995
Date Approved: September 25, 1997

G. GMP Inspection: May 20, 1997

H. Date of Notice of Approval to Applicant: September 25, 1997

II. Indications for Use

SILIKON 1000 is indicated for use as a prolonged retinal tamponade in selected cases of complicated retinal detachments where other interventions are not appropriate for patient management. Complicated retinal detachments or recurrent retinal detachments occur most commonly in eyes with proliferative vitreoretinopathy (PVR), proliferative diabetic retinopathy (PDR), cytomegalovirus (CMV) retinitis, giant tears, and following perforating injuries. SILIKON 1000 is also indicated for primary use in detachments due to Acquired Immune Deficiency Syndrome (AIDS) related CMV retinitis and other viral infections affecting the retina.

III. Contraindications

As silicone oil can chemically interact with and opacify silicon elastomers, the use of SILIKON 1000 is contraindicated in pseudophakic patients with silicone intraocular lenses. Use of SILIKON 1000 is contraindicated in patients with a known hypersensitivity to silicone oil.

IV. Warnings and Precautions

The warnings and precautions can be found in the labeling (Attachment 1).

V. Device Description

SILIKON 1000 is a sterile, highly purified long chain polydimethylsiloxane. It is a clear colorless liquid at room temperature with a nominal viscosity of 1000 centistokes (cs). SILIKON 1000 (purified polydimethylsiloxane) or α-(Trimethylsilyl)-ω-methylpoly[oxy(dimethylsilylene)] is a copolymer, having an average molecular weight of approximately 44,000, and is synthesized from dichlorodimethylsilane and chlorotrimethylsilane. SILIKON 1000 has a high surface tension (>21dynes/cm) and is immiscible with aqueous components. It has the following formula:

$$(CH_3)_3SiO\text{-}[(CH_3)_2SiO]_n\text{-}Si(CH_3)_3$$

It has a specific gravity between 0.96 and 0.98 g/cm^3 (25°C) and a refractive index between 1.402 and 1.405 (25°C). Low molecular weight siloxanes are ≤0.0200% (200 ppm) for each detectable cyclic or linear species. Terminal -OH end groups do not exceed 100 ppm. Each 1 mL contains solely polydimethylsiloxane oil in neat form.

SILIKON 1000 has the following physical and chemical specifications for finished product:

Specifications:

Viscosity (25°C)	900 - 1200 cs
Polydispersity (MW/MN)	< 2.5
Volatility (TGA @ 200°C)	< 1.0%
Volume resistivity	> 1 x 10^{15} Ohm cm
Low Molecular Weight Cyclic Siloxanes	≤ 200 ppm each
Weight Average Molecular Weight	38,000 - 48,000
Particulate matter (particules/ml)	≤ 50 @ ≤ 10 μm; ≤ 5 @ ≤ 25 μm
FT-IR	Complies to USP
Acidity	< 0.10 ml
Heavy Metals limit test	< 0.001 %
Sterility (USP)	Sterile
Bacterial endotoxins	≤ 0.5 EU/mL

SILIKON 1000 is supplied in 10 mL glass vials filled with 8.5mL of sterile silicone oil.

VI. Alternative Practices and Procedures

Silicone oil is used as a postoperative tamponade following vitreous surgery in cases of complicated retinal detachment either when previous attempts to reattach the retina have failed, or when the condition of the eye or of the patient makes surgery with alternative practices unlikely to succeed.

Conventional retinal surgery for retinal detachments consists of scleral buckle surgery (Custodis 1953, Schepens 1964, and Lincoff et al. 1965), sometimes accompanied by external drainage of subretinal fluid through a sclerotomy, and cryotherapy or laser photocoagulation of the edges of the retinal tears (Meyer-Schwickerath 1959 and Lincoff et al. 1964). These procedures are effective in most cases of primary retinal detachment. Some cases of retinal detachment present with conditions that make scleral buckling surgery less effective such as: posteriorly located retinal breaks, significant scar tissue on the surface or underneath the retina which exerts traction on the retina preventing reattachment, or optical problems which obstruct the view of the retina. In detachments complicated by these conditions, many such eyes can be treated successfully with vitrectomy techniques, during which the retina is repositioned into its normal location by endodrainage of subretinal fluid through holes in the retina during an exchange of the normal intraocular fluid contents for either air, or a long- acting gas (Fineberg et al. 1975, Machemer and Laqua 1978, Abrams et al. 1982, and Lucke and Laqua 1990).

Following initially successful retinal detachment surgery, intraocular scar tissue can proliferate to an extent that the scar tissue exerts enough traction on the retinal surface to cause retinal redetachment. This condition is called proliferative vitreoretinopathy (PVR). In order to repair detachments with significant amounts of PVR, the scar tissue must be peeled off of the retina (Machemer and Laqua 1978, Michels 1981, and Charles 1981). Following this membrane peeling, the retina is repositioned and the vitreous cavity is filled with an agent to act as a tamponade to keep the retina in its normal position while a chorioretinal scar is forming induced by photocoagulation or cryotherapy of the retina surrounding retinal tears. Various gas tamponades are used, such as perfluoropropane and sulfurhexafluoride (Lincoff et al. 1983, and Faulbourn and Bowald 1987). These intraocular gas bubbles gradually decrease in size. As the bubbles decrease in size, it becomes imperative that patients position their heads in order to keep the gas bubble opposed to the areas of the retinal breaks. If the retinal tears are inferior, the patient often must maintain strict face-down positioning for extended periods of time.

VII. Dosage and Administration

The Dosage and Administration of SILIKON 1000 can be found in the labeling under "Directions for Use" (Attachment 1).

VIII. Marketing History

SILIKON 1000 has not been marketed in the United States as an intraocular fluid.

IX. Potential Adverse Effects

The data supporting the rates of occurrence of adverse reactions were derived from the sponsored prospective U.S.-based multicenter clinical trial (2754 total eyes treated with 2573 Core Study eyes analyzed at 36 investigational centers), consisting of 757 CMV and 1816 non-CMV (PDR, Giant Tear, PVR and Trauma and 181 "other" diagnoses related retinal detachments which are not represented in the Core Study analyses). Comparative data from two other published studies conducted by other sponsors with silicone oils were considered in the analysis of safety and effectiveness. These included, (1) the National Eye Institute Silicone Study Group (Silicone Study Reports #1 and #2) and (2) the Lucke Study (Lucke K., Laqua H: *Silicone Oil in the Treatment of Complicated Retinal Detachments*, Springer-Verlag, Berlin, 161 pages, 1990).

The percentages reported below represent the range of occurrence for the SILIKON 1000 prospective study.

Table 1 - 6 Months and Last Examination for Safety Outcomes

OUTCOME	VISIT[1]	CMV	Non-CMV
Emulsification in eyes w/oil	6 month Last visit	1% 1%	3% 3%
Cataract in phakic eyes	6 month Last visit	64% 38%	63% 71%
Hypotony*	6 month[2] Last visit	6% 4%	19% 19%
Elevated IOP	6 month[3] Last visit	0% 1%	3% 5%
Corneal opacity/abrasion*	6 month[4] Last visit	6% 4%	26% 31%

* The rate of previous vitreoretinal operative procedures was 14% for CMV patients and 86% for non-CMV patients.

[1] The last visit may have occurred anytime post-operatively, and the 6 month visit may have occurred post-operatively between 137 and 272 days.

[2] Incidence rate of hypotony in non-CMV subjects at 6-months postoperatively was significantly greater in aphakic (21%) and pseudophakic (17%) eyes versus phakic (7%) eyes ($p < 0.01$).

[3] Incidence rate of elevated IOP in non-CMV subjects at 6-months postoperatively was significantly greater in phakic eyes (7%) versus aphakic (3%) and pseudophakic (2%) eyes ($p = 0.03$).

[4] Incidence rate of corneal opacity/abrasion in non-CMV subjects at 6-months postoperatively was significantly greater in aphakic (30%) and pseudophakic (21%) eyes versus phakic (8%) eyes ($p < 0.01$). Incidence rate of corneal opacity/abrasion in CMV subjects at 6-months postoperatively was significantly greater in aphakic (20%) and pseudophakic (11%) eyes versus phakic (4%) eyes ($p=0.04$).

Table 2 provides the safety and efficacy results at 6, 12, and 24 months stratified by complete attachment and macula attachment for Company A.

TABLE 2

TABLE 2 SILIKON 1000
Safety and Efficacy Results at 6, 12 and 24 Months
Stratified by Complete Attachment and Macula Attachment

OUTCOME	CMV Eyes			Non-CMV Eyes		
	6 mos. (N_T = 718) (n_{6mos} = 220) ($n_{6mos, CA}$ = 163) ($n_{6mos, MA}$ = 200)	12 mos. (N_T = 718) (n_{12mos} = 90) ($n_{12mos, CA}$ = 59) ($n_{12mos, MA}$ = 71)	24 mos. (N_T = 718) (n_{24mos} = 19) ($n_{24mos, CA}$ = 16) ($n_{24mos, MA}$ = 17)	6 mos. (N_T = 1669) (n_{6mos} = 1187) ($n_{6mos, CA}$ = 785) ($n_{6mos, MA}$ = 976)	12 mos. (N_T = 1669) (n_{12mos} = 886) ($n_{12mos, CA}$ = 568) ($n_{12mos, MA}$ = 711)	24 mos. (N_T = 1669) (n_{24mos} = 415) ($n_{24mos, CA}$ = 256) ($n_{24mos, MA}$ = 317)
Complete attachment	163/212 (77%)	59/79 (75%)	16/19 (84%)	785/1119 (70%)	568/820 (69%)	256/371 (69%)
Macula attachment	200/212 (94%)	71/77 (92%)	17/19 (89%)	976/1094 (89%)	711/818 (87%)	317/367 (86%)
Emulsification						
in eyes with oil remaining	2/195 (1%)	1/70 (1%)	0/17 (0%)	22/882 (2%)	14/577 (2%)	13/236 (6%)
and w/complete attach.	2/148 (1%)	1/54 (2%)	0/15 (0%)	17/580 (3%)	8/358 (2%)	8/137 (6%)
and w/macula attach.	2/184 (1%)	1/64 (2%)	0/16 (0%)	17/742 (2%)	12/473 (3%)	9/186 (5%)
Cataract in phakic eyes	110/172 (64%)	44/53 (83%)	2/2 (100%)	43/70 (61%)	33/45 (73%)	8/11 (73%)
in eyes w/complete attach.	82/128 (64%)	29/36 (81%)	2/2 (100%)	30/47 (64%)	22/30 (73%)	8/9 (89%)
in eyes w/macula attach.	100/160 (63%)	37/45 (82%)	2/2 (100%)	37/59 (63%)	28/38 (74%)	8/10 (80%)

Note: N_T is the total number of eyes treated; n_x is the number of eyes with an examination at time x; $n_{x, CA}$ is the number of eyes with complete attachment at examination x; $n_{x, MA}$ is the number of eyes with macula attachment at examination x.

TABLE 2

TABLE 2 CON'T . SILIKON 1000
Safety and Efficacy Results at 6, 12 and 24 Months
Stratified by Complete Attachment and Macula Attachment

OUTCOME	CMV Eyes			Non-CMV Eyes		
	6 mos. (N_T = 718) (n_{6mos} = 220) ($n_{6mos, CA}$ = 163) ($n_{6mos, MA}$ = 200)	12 mos. (N_T = 718) (n_{12mos} = 90) ($n_{12mos, CA}$ = 59) ($n_{12mos, MA}$ = 71)	24 mos. (N_T = 718) (n_{24mos} = 19) ($n_{24mos, CA}$ = 16) ($n_{24mos, MA}$ = 17)	6 mos. (N_T = 1669) (n_{6mos} = 1187) ($n_{6mos, CA}$ = 785) ($n_{6mos, MA}$ = 976)	12 mos. (N_T = 1669) (n_{12mos} = 886) ($n_{12mos, CA}$ = 568) ($n_{12mos, MA}$ = 711)	24 mos. (N_T = 1669) (n_{24mos} = 415) ($n_{24mos, CA}$ = 256) ($n_{24mos, MA}$ = 317)
Hypotony	10/183 (5%)	3/71 (4%)	2/17 (12%)	212/1094 (19%)	153/789 (19%)	59/374 (16%)
in eyes w/complete attach.	7/140 (5%)	2/50 (4%)	1/14 (7%)	118/732 (16%)	73/508 (14%)	23/240 (10%)
in eyes w/macula attach.	9/171 (5%)	3/60 (5%)	1/15 (7%)	150/911 (16%)	102/644 (16%)	32/296 (11%)
Elevated IOP	0/183 (0%)	1/71 (1%)	0/17 (0%)	30/1094 (3%)	31/789 (4%)	19/374 (5%)
in eyes w/complete attach.	0/140 (0%)	1/50 (2%)	0/14 (0%)	20/732 (3%)	21/508 (4%)	13/240 (5%)
in eyes w/macula attach.	0/171 (0%)	1/60 (2%)	0/15 (0%)	25/911 (3%)	24/644 (4%)	15/296 (5%)
Corneal opacity/abrasion	10/213 (5%)	8/82 (10%)	1/19 (5%)	298/1147 (26%)	257/851 (30%)	168/395 (43%)
in eyes w/complete attach.	8/161 (5%)	3/57 (5%)	0/16 (0%)	173/764 (23%)	125/547 (23%)	77/247 (31%)
in eyes w/macula attach.	10/198 (5%)	3/68 (4%)	0/17 (0%)	221/945 (23%)	170/688 (25%)	104/304 (34%)

Note: N_T is the total number of eyes treated; n_x is the number of eyes with an examination at time x; $n_{x, CA}$ is the number of eyes with complete attachment at examination x; $n_{x, MA}$ is the number of eyes with macula attachment at examination x.

Unanticipated Adverse Events: A single unanticipated adverse event was reported, namely, an allergic reaction to silicone. This event, however, did not represent the subject's initial exposure to silicone. The subject had a prior scleral buckle procedure and a silicone IOL implanted which was believed to be causing chronic inflammation at the time of retinal detachment surgery with silicone oil instillation. The silicone IOL was removed during the retinal detachment surgery with silicone oil instillation. Postoperatively the subject developed severe uveitis similar to that experienced after insertion of the scleral buckle and silicone IOL. Medication was administered and the inflammation subsided in approximately 3 weeks and cleared 3.5 months postoperatively at which time the subject was taken off medication for the inflammation. This subject's visual acuity was HM preoperatively, and improved to 20/400 at 6 months postoperatively with a completely attached retina, clear cornea, and IOP of 10.

No other unanticipated adverse events were reported by any of the study sites during the period of the study.

X. Summary of Pre-clinical Studies

A number of publications are presented which address various chemical and biological properties of the SILIKON 1000.

1. Safety and Toxicity Studies. Ocular toxicity of silicone oils has been alleged, but not been proven to be related to the presence of unreacted low molecular weight components (LMWC's) and residual catalysts, both of which appear to affect ocular tissue in a dose dependent fashion (Gabel et al. 1987, Parel 1989, and Nakamura et al. 1991). The LMWC's include both linear and cyclic siloxanes, such as hexamethyldisiloxane, octamethyltrisiloxane, decamethyltetrasiloxane, hexamethylcyclotrisiloxane (D_3), octamethylcyclotetrasiloxane (D_4), and decamethylcyclopentasiloxane (D_5). These impurities in the SILIKON are kept at very low levels, including direct measurement of LMWC's; volatility (reflects the presence of small molecular weight components which can diffuse into adjacent tissues); resistivity (reportedly an index of ionic components of catalyst residues); and, measurement of reactive -OH end groups. A series of investigators have examined the emulsification potential of silicone oils as related to their physical properties (Crisp et al. 1987; Gabel et al. 1987; Gabel 1989; Petersen and Rizau-Tondrow 1988; Mukai et al. 1972; and Ohira et al. 1988). In these studies the tendency for the oil to emulsify was attributed to factors which lower the interfacial tension of the oil, such as high levels of impurities left from processing, low viscosity, and low molecular weight contaminants. Other factors such as tissue debris and blood would have an adverse effect on interfacial surface tension. A very low rate (1- 3%) of emulsification was reported in this clinical study.

2. In Vivo and In Vitro Tests:

MEM Elution Cytotoxicity with Endpoint Titration Assay: Silicone oil was eluted with MEM cell culture medium or saline. Extract is plated onto test monolayer containing mouse L929 cells. Summary: Not reactive (non toxic).

Guinea Pig Maximization: Silicone oil extracted using saline. Summary: Not sensitizing.

Ames Mutagencity: Silicone Oil extracted using solvent, then serially diluted to 0.1, 0.01, 0.001, and 0.0001. Solutions were plated with tester stains; tester stains were : TA98, TA100, TA1535, TA1537 and TA1538; the plating was done in duplicate, both with and without S9 (rat liver microsomes). Summary: Not mutagenic.

In vitro cytotoxicity studies by MEM Elution on both the raw material and finished product show that SILIKON 1000 would not be considered toxic to L-929 mouse connective tissue cells and thus demonstrates its biocompatability. Guinea pig maximization (Kligman) test results indicated no contact dermal allergenicity. Ames Mutagenicity testing also indicated no toxicity. The effects of various silicone oils on corneal endothelial cell permeability has been studied (Norman 1990, and Green 1993) and SILIKON 1000 was found to cause the least passive increases in permeability to inulin or dextran.

Based on these studies, SILIKON 1000 has the appropriate physical and chemical properties for the stated indications for use and is considered safe for use in those indications.

3. Chemical Equivalency. During the course of the study, the raw material supplier changed. Chemical equivalency of the two raw material suppliers were tested (hereinafter referred to as Company A and Company B). A confirmation clinical study was conducted to demonstrate comparable clinical outcomes of silicone oil manufactured from the two suppliers.

4. Sterilization. SILIKON 1000 is supplied in single 10 mL glass vials filled with 8.5mL of sterile silicone oil, capped with a stopper, sterilized by dry heat sterilization,

and packaged inside non-sterile polybags intended for single use only. SILIKON 1000 contains no preservatives.

5. Shelf Life Dating. The shelf life testing results support a 10 month shelf life for SILIKON 1000. A shelf-life and stability protocol is approved.

XI. Summary of Clinical Studies

2754 eyes were enrolled and treated with SILIKON 1000 under the manufacturers investigational device exemptions (IDE) application. SILIKON 1000 was also studied in 12 individual investigator IDE's. The SILIKON 1000 study was conducted during five years at 78 sites (42 emergency use only and 36 primary sites) by 182 physicians. The key measures of effectiveness were retinal reattachment and preservation of visual acuity. The key measures of safety were the time until development and incidence of complications such as corneal opacity, increased intraocular pressure, or formation of a cataractous lens.

A. Clinical Studies

The data upon which SILIKON 1000 claims of safety and effectiveness are based consists of a 2573 patient eyes prospective clinical evaluation conducted at 36 investigational centers between August 1991 and January 1997 (2754 total eyes treated - 181 eyes with "other" diagnoses were not represented in the Core Study analyses).

1. Objective. The objective of this study was to evaluate the acute and long-term ocular safety and effectiveness of SILIKON 1000 in the treatment of complicated retinal detachments due to proliferative vitreoretinopathy (PVR), proliferative diabetic retinopathy (PDR), traumatic perforating injury, giant tears, and HIV-related CMV retinitis. This was an open-label, non-comparative study.

2. Study Design. This clinical investigation was designed as an open-label, non-comparative study for Company A. The objective of this study was to establish whether or not SILIKON 1000 is a safe and effective retinal tamponade for the management of complicated retinal detachments.

During this study, the raw material supplier changed thus, the sponsor was required to conduct a confirmatory study. Comparable clinical performance was demonstrated as assessed with non-CMV eyes during the clinical trial.

3. Study Population and Demographics. Patients with complex retinal detachments that have already been treated with conventional procedures such as scleral buckling, vitrectomy with fluid/gas exchange, and endophotocoagulation, which have failed were eligible for enrollment. In addition, patients whose condition was so severe that these techniques were given no hope of success were also considered eligible. The

underlying etiologies of eligible cases were PVR following failed rhegmatogenous retinal detachment surgery, complex retinal detachments of the proliferative retinopathies, giant retinal tears and complicated cases of trauma not treatable with conventional methods. AIDS patients with retinal detachments secondary to necrotizing retinitis were also included. There was no age limit specified.

The following definitions of etiologies of eligible cases:

CMV:	AIDS patients with retinal detachments secondary to necrotizing retinitis.
PDR :	Eyes with proliferative diabetic retinopathy (PDR) with or without proliferative vitreoretinopathy (PVR).
GIANT TEAR :	Eyes with giant tear with or without PVR.
PVR:	Eyes with PVR with or without other complications.
TRAUMA:	Eyes with trauma with or without PVR not treatable with conventional methods.
OTHER:	Eyes with other heterogeneous etiologies and/or diagnoses.
NON-CMV:	Group comprised of PDR, PVR, TRAUMA and GIANT TEAR eyes.

Preoperative data included demographic information (gender and age), general medical and ocular history, and an ocular evaluation (best corrected visual acuity, intraocular pressure (IOP), and status of the anterior and posterior segment). Operative data were collected on the procedures used including fluid/gas exchange, scleral buckle, and retinotomy. Postoperative data included best corrected visual acuity, status of the retina and macula, and complications and were collected at one week, one month, three months, six months, one year and two years. An exit form was completed when the patient completed the two year study schedule, was unable to complete the study, or expired. An adverse event form was completed if a serious unanticipated adverse reaction occurred.

There were 2754 total eyes treated with 2573 Core eyes analyzed in this study. The HIV-related CMV retinitis indication included 757 eyes, and the non-CMV indications included 935 cases of proliferative vitreoretinopathy (PVR), 359 cases of proliferative diabetic retinopathy (PDR), 291 cases of trauma, and 231 giant tears. There were an additional 181 eyes treated with SILIKON 1000 (purified polydimethylsiloxane) for diagnoses other than those detailed above which were not represented in the Core Study analyses.

As of January 1997, 454 (60%) of the 757 CMV retinitis Core Study eyes had a 3 month postoperative follow-up examination, whereas 1289 (71%) of the 1816 non-CMV Core Study eyes had a 6 month examination. The average time in the study for Core eyes was 4.5 (range 0 to 6 months) and 13 months (range 0 to 52 months) for CMV and non-CMV eyes, respectively.

Subject average ages were 39 years of age for CMV patients and 49 years of age for non-CMV patients. Males comprised 67% of the non-CMV population and a larger portion (90%) of the CMV population. A summary table of pre-operative demographics is presented in Table 3.

TABLE 3: Summary of Pre-operative Baseline Characteristics: Core

Characteristic	CMV	Non-CMV	PDR	Giant Tear	PVR	Trauma
No. Patients	659	1780	340	225	926	289
No. Eyes	757	1816	359	231	935	291
Age (mean±SD)	39.1±10.0	49.4±23.7	47.5±17.3	37.3±23.0	58.3±22.2	32.8±21.7
Gender						
Female	73 (11%)	607 (34%)	167 (49%)	49 (22%)	332 (36%)	60 (21%)
Male	586 (89%)	1172 (66%)	173 (51%)	176 (78%)	594 (64%)	229 (79%)
Visual Acuity						
Ambulatory	459 (64%)	247 (14%)	54 (15%)	33 (15%)	137 (15%)	23 (8%)
IOP (mm Hg)						
≤ 5 (hypotony)	36 (6%)	357 (22%)	43 (12%)	59 (30%)	192 (22%)	63 (26%)
≥ 30 (elevated)	0 (0%)	37 (2%)	18 (5%)	3 (2%)	10 (1%)	6 (2%)
Corneal Status						
Opacification/abrasion	14 (2%)	325 (19%)	49 (14%)	46 (21%)	121 (14%)	109 (40%)
Cataract in phakic eye	30 (4%)	348 (56%)	125 (58%)	48 (56%)	115 (51%)	60 (59%)

4. Surgical Procedure and Follow-up. Operative procedure varied according to the surgeons' preferences, generally consisting of pars plana vitrectomy, relief of all retinal traction, and reattachment by fluid-air exchange using a drainage retinotomy. In some cases, fluid-silicone exchange was employed for silicone oil instillation. In these cases, the retina was flattened during the exchange procedure. Some eyes also underwent retinopexy, scleral buckling, or lensectomy (in phakic patients the necessity for lens extraction was evaluated based on the estimated duration of the tamponade). The vitreous cavity was then filled with silicone oil to the iris plane. In aphakic patients an iridectomy at the 6 o'clock position was usually performed.

Following silicone oil injection, examinations were to be conducted at intervals of 1 week, 1, 3, 6, 12, and 24 months, or more frequently if required for management of complications due to the treatment or for management of the particular ocular pathology. The silicone oil was removed when, in the judgment of the investigator-surgeon, reattachment of the retina had occurred and further tamponade was no longer required.

5. Efficacy and safety endpoints. Efficacy was measured both by anatomic success, defined as complete retinal attachment or macular attachment, and by visual acuity success, defined as preservation of visual acuity or ambulatory vision. Safety variables were determined by the rate of complications including abnormal intraocular pressure, corneal or lens opacification.

Anatomic success was defined to be:
a) the percent of retinas completely attached posterior to the encircling buckle if present, and
b) the percent of attached maculas.

Visual acuity success was defined to be:
a) the percent of eyes with preservation (no loss) of visual acuity, and
b) the percent of eyes with ambulatory vision.

For the purposes of data analysis, visual acuities were graded in nine steps following a modification of the method suggested by Lucke and Laqua:

Visual Acuity Groups

Group	Lucke Categories	Snellen Equivalents
8	1.2 - 0.76	20/20 - 20/25
7	0.75 - 0.36	20/30 - 20/50
6	0.35 - 0.16	20/60 - 20/128
5	0.15 - 0.06	20/130 - 20/300
4	0.05 - 0.04	10/200 - 7/200
3	0.03 - 0.02	10/300 - 3/200
2	CF/HM	count fingers/hand movement
1	LP	light perception
0	NLP	No light perception

Using this table, preservation of visual acuity was defined to be a postoperative visual acuity in the same or higher group than the preoperative visual acuity. Ambulatory vision was defined to be a visual acuity $\geq$ 1/50 (i.e., group 3 or higher).

Safety variables were characterized by complications, including hypotony, elevated IOP, corneal abnormalities, and lens opacification. Normal IOP was defined to be in the range 6-25 mm Hg. Hypotony was defined to be IOP $\leq$ 5 mm Hg, and elevated IOP was defined to be IOP $\geq$ 30 mm Hg.

6. Equivalence of safety and efficacy endpoints: Fisher's Exact tests were carried out to compare outcomes at 6 months and at the last examination between eyes treated with SILIKON 1000 supplied by Company A or Company B.

For non-CMV eyes, all safety and efficacy outcomes were equivalent between the Company B population and the Company A population at 6 months and at the last examination; no statistically significant differences were found in any of the outcomes between the two populations

For CMV eyes, the 6 month rate of corneal opacity was greater for the population of Company B eyes than it was for Company A eyes (19% vs 5% respectively, $p = 0.05$). However, the 19% rate of corneal opacity for Company B CMV eyes was less than that reported for non-CMV eyes treated with either Company B or Company A (28% and 26%, respectively). Further, at the last examination, the rates of corneal opacity were equivalent between the population of Company B eyes and Company A eyes (6% vs. 4%, $p = 0.65$). No other statistically significant differences were found in any of the safety or efficacy parameters.

These analyses concludes that the two suppliers (Company A and Company B) of

SILIKON 1000 are clinically equivalent for the following reasons:

1. For non-CMV eyes, no statistically significant differences were found in any of the safety and efficacy outcomes between the populations of Company A and Company B.

2. For CMV eyes, although the 6 month rates of complete attachment and corneal opacity were greater for the population of Company B eyes than for Company A eyes, these rates were equivalent between the two populations at the last examination. No other statistically significant differences were found in any of the safety and efficacy outcomes between the populations of Company A and Company B eyes.

7. Combined Safety and Efficacy Data from Company A and Company B

A. Combined Safety and Efficacy Data at 6, 12, and 24 Month: Attachment rates were stable across the three follow-up periods (6, 12 and 24 months), Table 4. For CMV eyes, the percentages of eyes with complete attachment were 78% (6 month exam), 75% (12 month exam) and 84% (24 month exam). For non-CMV eyes these percentages were 70%, 69% and 69%, respectively. For CMV eyes the percentages of eyes with macular attachment were 95% (6 month exam), 92% (12 month exam) and 89% (24 month exam); for non-CMV eyes these percentages were 89%, 87%, and 86% respectively.

For CMV eyes, the percentage of eyes with postoperative corneal opacities remained very small (6%, 10%, 5% at 6, 12, and 24 most, respectively). In contrast, for non-CMV eyes, the percentage of eyes with postoperative corneal opacities increased from 26% at 6 months to 42% at 24 month. The increase in postoperative corneal opacity is an expected outcome for non-CMV eyes and can be explained by contact of silicone oil in the anterior chamber with the corneal endothelium. The rates of corneal opacity in these eyes is comparable to those reported in other studies. For both CMV and non-CMV eyes, the percentages of eyes with elevated IOP was stable across the period of follow-up and was very small. The percentage of CMV eyes with hypotony at 6 months remained stable and was very small. For non-CMV eyes, the rate of hypotony at 6, 12 and 24 months was lower than that reported preoperatively.

A large percentage of phakic eyes, having either preoperative or postoperative cataract, remained stable. Cataract extraction with intraocular lens implantation was successfully performed without silicone oil removal. The low rate of silicone oil emulsification in both CMV and non-CMV eyes was notable.

Table 4
Longitudinal Analysis of Core at 6, 12, and 24 Months

OUTCOME	CMV Eyes 6 mos.	CMV Eyes 12 mos.	CMV Eyes 24 mos.	Non-CMV Eyes 6 mos.	Non-CMV Eyes 12 mos.	Non-CMV Eyes 24 mos.
Complete attachment	178/228 (78%)	61/81 (75%)	16/19(84%)	855/1219 (70%)	579/836 (69%)	256/371 (69%)
Macula attachment	216/228 (95%)	73/79 (92%)	17/19 (89%)	1062/1189 (89%)	726/833 (87%)	317/367 (86%)
Ambulatory vision	151/234 (65%)	46/91 (51%)	10/19 (53%)	480/1251 (38%)	303/862 (35%)	126/402 (31%)
Preserved vision	106/230 (46%)	33/89 (37%)	6/19 (32%)	1035/1229 (84%)	675/846 (80%)	309/393 (79%)
Emulsification	3/211 (1%)	1/72 (1%)	0/17 (0%)	29/959 (3%)	20/585 (3%)	13/236 (5%)
Cataract	118/185 (64%)	44/53 (83%)	2/2 (100%)	50/80 (63%)	33/45 (73%)	8/11 (73%)
Hypotony	11/196 (6%)	3/72 (4%)	2/17 (12%)	228/1196 (19%)	155/805 (19%)	59/374 (16%)
Elevated IOP	0/196 (0%)	1/72 (1%)	0/17 (0%)	35/1196 (3%)	31/805 (4%)	19/374 (5%)
Corneal opacity/abrasion	13/229 (6%)	8/82 (10%)	1/19 (5%)	326/1248 (26%)	257/851 (30%)	168/395 (42%)

TABLE 4

B. A Combined Safety and Efficacy Data at 6 months and Last Examination: Summary of all safety and efficacy data for the combined cohort is presented in Table 5.

For CMV eyes, the percentages of eyes with complete attachment were 78% (6 month exam) and 80% (last exam); for non-CMV eyes these percentages were 70% and 69%, respectively. For CMV eyes, the percentages of eyes with macular attachment were 95% (6 month exam) and 94% (last visit); for non-CMV eyes these percentages were 89% and 87%, respectively.

Visual acuity outcomes at the 6 month and last examination were also comparable. For non-CMV eyes, there was a marked increase in the percentage of eyes with postoperative ambulatory vision. For example, for PDR eyes the percentage of eyes with ambulatory vision increased from 15% (preoperatively) to 33% (at 6 month postoperatively).

For other non-CMV eyes, the percentages increased from 15% to 43% (Giant tears), 15% to 40% (PVR), and 8% to 35% (trauma). These increases in the percentages of eyes with ambulatory vision are also reflected in the large percentages of eyes with preservation of vision. In contrast, the increase in the percentage of CMV eyes with ambulatory vision was less dramatic. This can be explained by the fact that CMV eyes had better preoperative vision than non-CMV eyes. The large percentage of CMV eyes with preserved vision is indicative of the fact that vision is maintained in CMV eyes with preoperative ambulatory vision.

For CMV eyes, the percentage of eyes with preoperative and postoperative corneal opacities is very small (2% vs. 6%). In contrast, for non-CMV eyes, the percentage of eyes with postoperative corneal opacities increased from 19% to 26%. The large percentage of preoperative corneal opacity can be explained by the large percentage of eyes with at least one or more previous operations. The rate of previous vitreoretinal operative procedures was 14% (n=108/757) for CMV patients and 86% (n=1562/1816) for non-CMV patients. Postoperative corneal opacity is an expected outcome for non-CMV eyes and can be explained by the presence of silicone oil in the anterior chamber in contact with the corneal endothelium. Notwithstanding, the rates of corneal opacity in these eyes are comparable to those reported in other studies.

For both CMV and non-CMV eyes, the percentages of eyes at 6 months with elevated IOP was very small (0% for CMV eyes, 3% for non-CMV eyes). Eyes at risk for developing elevated IOP are those with penetrating injury or those that have suffered anterior chamber angle damage as a result of complicated lens extraction.

For CMV eyes, the percentage of eyes with hypotony at 6 months was very small (6%). For non-CMV eyes, the rate of hypotony at 6 months was lower than that reported preoperatively (22% vs. 19%). Hypotony is a postoperative complication associated with retinal detachment and surgery for retinal detachment, and has not been associated with the use of silicone oil as a retinal tamponade.

Finally, it is important to note the low rate of silicone oil emulsification in both CMV and non-CMV eyes. At 6 months, only 2 CMV eyes (<1%) and 25 non-CMV eyes (2%) had emulsification of oil.

Table5: Combined Safety and Efficacy results at 6 Months and at the Last Examination

OUTCOME	VISIT	CMV	Non-CMV	PDR	GNT TEAR	PVR	TRAUMA
Complete attachment	6 month Last visit	178/228 (78%) 541/679 (80%)	855/1219 (70%) 1107/1611 (69%)	135/221 (61%) 171/302 (57%)	114/164 (70%) 152/213 (71%)	485/640 (76%) 627/838 (75%)	121/194 (62%) 157/258 (61%)
Macula attachment	6 month Last visit	216/228 (95%) 633/672 (94%)	1062/1189 (89%) 1363/1570 (87%)	172/216(80%) 218/293(74%)	141/157(90%) 181/206(88%)	586/631(93%) 751/823(91%)	163/185(88%) 213/248(86%)
Ambulatory vision	6 month Last visit	151/234(65%) 441/696(63%)	480/1251(38%) 564/1724(33%)	80/245(33%) 84/347(24%)	68/159(43%) 82/211(39%)	265/655(40%) 320/891(36%)	67/192(35%) 78/275(28%)
Preserved vision	6 month Last visit	106/230(46%) 344/679(51%)	1035/1229(84%) 1333/1689(79%)	171/243(70%) 220/343(64%)	137/153(90%) 173/203(85%)	557/644(86%) 717/872(82%)	170/189(90%) 223/271(82%)
Emulsification in eyes w/oil	6 month Last visit	3/211(1%) 5/655(1%)	29/959(3%) 40/1154(3%)	171/243(70%) 220/343(64%)	5/111(5%) 6/133(5%)	10/518(2%) 21/601(3%)	9/145(6%) 6/173(1%)
Cataract in phakic eyes	6 month Last visit	118/185(64%) 228/602(38%)	50/80(63%) 82/116(71%)	23/34(68%) 42/53(79%)	6/9(67%) 5/8(63%)	15/29(52%) 25/40(63%)	6/8(75%) 10/15(67%)
Hypotony	6 month Last visit	11/196(6%) 24/583(4%)	228/1196(19%) 313/1632(19%)	50/235(21%) 63/323(205)	24/142(17%) 31/200(16%)	119/634(19%) 16/853(18%)	35/185(19%) 63/256(25%)
Elevated IOP	6 month Last visit	0/196(0%) 3/583(1%)	35/1196(3%) 80/1632(5%)	14/235(6%) 31/323(10%)	3/142(2%) 7/200(4%)	14/634(2%) 35/853(4%)	4/185(2%) 7/256(3%)
Corneal opacity/abrasion	6 month Last visit	13/229(6%) 27/687(4%)	326/1248(26%) 526/1713(31%)	52/234(22%) 97/335(29%)	44/161(27%) 57/214(27%)	165/656(25%) 253/883(29%)	65/197(33%) 119/281(42%)

8. Comparison to retrospective Silicone Oil Studies: Safety and efficacy outcomes at the 6 month (cohort) and last examination (core) were compared to the Silicone study and the Lucke-Laqua study (Tables 6 and 7). From those analyses, it was concluded that results for SILIKON 1000 compared favorably with those reported in the Silicone study and the Lucke-Laqua study.

9. Cataractogenesis of 1000 cs versus 5000 cs: Regarding the possibility of greater cataractogenesis in AIDS patients treated with 1000 cs, as opposed to 5000 cs showed that the median time to development of cataract in patients treated with 1000 cs was 180 days and in patients implanted with 5000 cs, 225 days.

10. Analysis of reinjections: For Company A, 46 CMV and 209 non-CMV eyes had a single reinjection, while 1 CMV and 24 non-CMV eyes had 2 re-injections. 3 non-CMV eyes underwent reinjections three times. For Company B, 2 CMV and 10 non-CMV eyes had a single reinjection, while 2 non-CMV eyes had re-injection twice.

11. Analysis of oil removal: The table below summarizes the number of eyes and the time of oil removal by diagnosis.

Table 8: Profile of oil removal

OIL	VISIT	CMV	Non-CMV	PDR	GIANT TEAR	PVR	TRAUMA
Company A	< 6 month	4	232	42	41	104	45
	Last exam	6	376	7	70	219	80
Company B	< 6 month	0	17	2	4	10	1
	Last exam	0	25	3	4	13	5

Silicone oil was removed in slightly more than 10% of all eyes in the study with only 1% of the CMV population eyes having oil removed. Oil was generally removed within the first 3 to 6 months after treatment, based on surgeon assessment for stability of the retinal reattachment.

Table 6

Comparison of SILIKON 1000 to Lucke-Laqua "Early Group" Results

OUTCOME	VISIT	PDR		GIANT TEAR		TRAUMA	
		S1000	L-L	S1000	L-L	S1000	L-L
Complete attachment	6 month	61%	75%	70%	82%	62%	69%
	Last visit	57%	71%	71%	80%	61%	54%
Macula attachment	6 month	80%	NR	90%	NR	88%	NR
	Last visit	74%	NR	88%	NR	86%	NR
Ambulatory vision	6 month	33%	67%	43%	65%	35%	46%
	Last visit	24%	50%	39%	59%	28%	46%
Preserved vision	6 month	70%	71%	90%	69%	90%	77%
	Last visit	64%	58%	85%	55%	82%	50%
Emulsification	6 month	3%	NR	5%	NR	6%	NR
	Last visit	3%	NR	5%	NR	1%	NR
Cataract in phakic eyes	6 month	68%	NR	67%	NR	75%	NR
	Last visit	79%	NR	63%	NR	67%	NR
Hypotony	6 month	21%	NR	17%	NR	19%	NR
	Last visit	20%	NR	16%	NR	25%	NR
Elevated IOP	6 month	6%	NR	2%	NR	2%	NR
	Last visit	10%	NR	4%	NR	3%	NR
Corneal opacity/abrasion	6 month	22%	NR	27%	NR	33%	NR
	Last visit	29%	NR	27%	NR	42%	NR

TABLE 6

TABLE 7

Table 7
Comparison of SILIKON 1000 Results in Eyes with PVR to Other Studies

OUTCOME	VISIT	RICHARD JAMES S1000	SILICONE STUDY GROUP 1/1	SILICONE STUDY GROUP 1/2	SILICONE STUDY GROUP 2	LUCKE LAQUA "EARLY"
Complete attachment	6 month	76%	60%	70%	60%	66%
	Last visit	75%	60%-70%	64%	61%	57%
Macula attachment	6 month	93%	80%	80%	80%	NR
	Last visit	91%	65%-75%	78%	77%	NR
Ambulatory vision	6 month	40%	61%	60%	50%	48%
	Last visit	36%	50%-60%	45%	33%	46%
Preserved vision	6 month	86%	NR	NR	NR	60%
	Last visit	82%	NR	NR	NR	42%
Emulsification	6 month	2%	NR	NR	NR	NR
	Last visit	3%	NR	NR	NR	NR
Cataract in phakic eyes	6 month	52%	NR	NR	NR	NR
	Last visit	63%	NR	NR	NR	NR
Hypotony	6 month	19%	10%	10%	20%	NR
	Last visit	18%	11%	16%	22%	NR
Elevated IOP	6 month	2%	NR	NR	NR	NR
	Last visit	4%	0%	2%	3%	NR
Corneal opacity/abras'n	6 month	25%	20%	15%	40%	NR
	Last visit	29%	21%	30%	43%	NR

In addition, the following table summarizes changes in outcomes pre- to post- removal for Company B SILIKON 1000 for non-CMV.

Table 9: Company A SILIKON 1000 Non-CMV Eyes Change in Outcomes Pre- to Post-Removal

Time of removal (months)	#Eyes/ #Procedures	#Eyes Followed	Vision Loss	Redetach	Abnormal IOP	Abnormal Cornea
0-3	143/144	133	15(11%)	9(7%)	25(19%)	23(17%)
4-6	158/160	151	27(18%)	8(5%)	19(13%)	32(21%)
7-12	125/132	115	7(15%)	4(3%)	16(14%)	10(9%)
13-24	56/58	48	6(13%)	2(4%)	3(6%)	8(17%)

Time of Removal: time from first injection to last oil removal
Pre-Removal: examination prior to last oil removal
Post-Removal: last follow-up examination after oil removal
Vision Loss: change in visual acuity of one or more lines from pre- to post-removal
Retinal Redetachment: retina changed from completely or partially attached to completely detached
IOP or Corneal Abnormality: change from normal to abnormal from pre- to post-removal

12. Gender Analysis. A gender analysis was performed using the 2573 Core eyes (Table 10). There were no statistically significant differences regarding gender within CMV and non-CMV group eyes for safety parameters, such as rate of cataract formation in phakic eyes, changes in intraocular pressure (elevated or depressed), and oil emulsification, except for the rate of hypotony being greater in female CMV eyes (25%) versus male CMV eyes (2%). Because of the small sample size and the numerous and diverse complications with which these subjects' eyes presented, no definitive conclusions can be stated based on these findings.

TABLE 10: Comparison of 6 Month Outcomes Between Genders: Core

OUTCOME	GENDER	CMV	P	Non-CMV	P
Complete attachment	Female	25/33 (75%)	0.82	294/411 (71%)	0.47
	Male	153/195 (78%)		560/807 (69%)	
Macula attachment	Female	29/33 (88%)	0.08	362/404 (90%)	0.84
	Male	187/195 (96%)		699/784 (89%)	
Ambulatory vision	Female	17/33 (52%)	0.11	148/426 (35%)	0.07
	Male	134/201 (67%)		331/824 (40%)	
Preserved vision	Female	11/33 (33%)	0.13	351/420 (84%)	0.68
	Male	95/197 (48%)		683/808 (85%)	
Emulsification	Female	0/30 (0%)	0.99	11/350 (3%)	0.84
	Male	3/181 (2%)		18/608 (3%)	
Cataract in phakic eyes	Female	13/22 (59%)	0.64	18/26 (69%)	0.46
	Male	105/163 (64%)		32/54 (59%)	
Hypotony	Female	7/28 (25%)	0.01	87/403 (22%)	0.12
	Male	4/168 (2%)		141/792 (18%)	
Elevated IOP	Female	0/28 (0%)	0.99	8/403 (2%)	0.21
	Male	0/28 (0%)		27/792 (3%)	
Corneal opacity/abras.	Female	1/32 (3%)	0.99	113/421 (27%)	0.68
	Male	12/197 (6%)		213/826 (26%)	

XII. Conclusion Drawn From the Studies

A. Discussion of Valid Scientific Evidence. In accordance with 21 CFR 860.7 the validity of the evidence presented in this Premarket Approval (PMA) application was based upon an objective trial without a matched control. The clinical investigators were vitreoretinal surgeons with long standing experience in the standard methodologies for retinal reattachment procedures. Comparative study designs were considered, but rejected due to ethical considerations and the severe nature of the retinal disease in these study subjects.

B. Benefits of Silicone Oil Tamponade.

1. Duration of tamponade. Rates of retinal and macular reattachment comparable to other available products employed as long as 1-2 years with the benefit of no need for repeated intraocular injections (i.e., the half-lives of intraocular air and SF_6 bubbles are 2 and 4 days, respectively, and the longest half-life with other gases such as C_3F_8 is 20 days).

2. Optical properties. SILIKON 1000 is optically clear. This property allows for good vision through the bubble as early as in the immediate post-operative period, particularly in aphakic patients. Because the oil forms a convex surface near the pupil, the hyperopia experienced by aphakic patients is corrected and the eye becomes myopic (to about +5 diopters residual refraction).

3. Mobility of the patient. Changes in the external atmospheric pressure have no influence on the properties of silicone oil that has been instilled into the eye. Therefore, airline travel is not precluded for patients who receive silicone oil, in contrast to patients receiving a gas tamponade. These properties and the optical properties of the silicone oil mean that ambulatory visual acuity usually returns earlier in the course of recovery, usually immediately postoperatively, than with intraocular gas tamponade, which usually requires removal of the gas prior to recovery of ambulatory visual acuity.

4. Benefits of 1000 cs versus 5000 cs: Increased flow rate of 1000cs silicone oil at a given pressure allows for instillation and removal at much lower pressures than 5000cs oil. There are several reasons why this is advantageous:

1) Decrease of instillation and removal times allows for easier control of operative intraocular pressure.
2) Oil removal can be achieved by freely floating it to the eye, rather than requiring active suction at high pressure.
3) A pump is not mandatory for instillation or removal.

4) An out-patient setting is sufficient for postoperative addition or removal of a small quantity of 1000cs oil.
5) Risk of failure of tubing connections to a syringe or infusion cannula is reduced.

C. Risks of Silicone Oil Tamponade

1. General health. There have been no reports of SILIKON causing any adverse event as related to the general health of the patient. The PMA contained a literature search of all silicone oil publications as related to retinal detachment surgery in humans. There were no references to any systemic problems and no mention of migration of silicone oil outside the orbit.

2. Ocular complications. Treatment with SILIKON resulted in several known and expected ocular complications within 6 to 12 months after treatment. These included cataract in phakic patients (more than 60% of subjects), corneal opacity (6 - 26%), hypotony (6 - 19%), elevated intraocular pressure (0 - 3%), and oil emulsification (1 - 3%). Each of these complications can be treated either with devices, surgically, or with medication; cataract by lens removal and intraocular lens placement; corneal opacity by chelator treatment or corneal graft surgery; elevated IOP by anti-glaucoma drugs or filtration surgery; and, oil emulsification by silicone removal and replacement. Therefore, although posing a threat for eventual loss of visual acuity, these complications can be treated and are of relatively lower risk in view of the action of silicone oil to decrease the incidence of complete and rapid loss of vision due to retinal detachment.

D. Conclusion

In conclusion, the relative benefit-to-risk of SILIKON 1000 was based on the following:

1. an acceptable chance for restoration or maintenance of ambulatory vision;

2. advantage over the use of gases in its extended duration of tamponade for patients with these complicated detachments in that, for long-term tamponade, the silicone oil will remain until the oil is removed; and,

3. availability of treatment for many of the ocular complications resulting from the use of the silicone oil.

XIII. Panel Recommendations At an advisory meeting on January 13, 1997, the Ophthalmic Devices Panel unanimously recommended that Richard-James, Inc. PMA for SILIKON 1000 be approved.

XIV. CDRH Decision On February 22, 1995, CDRH granted expedited review for SILIKON 1000 because 1000cs may be significantly easier to use; has lower viscosity and is potentially easier to instill and remove from the eye; and the severity of the retinal conditions. CDRH has determined that, based on the data submitted in the PMA, there is reasonable assurance that SILIKON 1000 is safe and effective for its intended use, and issued an approval order on September 25, 1997.

XV. Approval Specifications The applicant's contract manufacturing facility was inspected from May 12 - 16, 1997, and was found to be in compliance with the device Good Manufacturing Practice regulation on May 20, 1997.

XVI. REFERENCES

CMV

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SILIKON 1000
(purified polydimethylsiloxane)

DESCRIPTION

SILIKON 1000 (purified polydimethylsiloxane) is a highly purified long chain polydimethylsiloxane trimethylsiloxy terminated silicone oil. It is sterile, non-pyrogenic, clear, colorless and has a viscosity of 1000 cs. for use as a postoperative retinal tamponade during vitreoretinal surgery. SILIKON 1000 is composed of silicon, oxygen, carbon and hydrogen atoms. SILIKON 1000 is immiscible with aqueous components and is a relatively inert material with little biological toxicity potential.

The structure of the molecule is:

$$(CH_3)_3SiO\text{-}[(CH_3)_2SiO]_n\text{-}Si(CH_3)_3$$

SILIKON 1000 is optically clear. The physical properties of SILIKON 1000 are listed below.

Viscosity (centistoke @ 25 °C):	1000 nominal
Refractive Index:	1.40
Specific Gravity (grams/cc):	0.97

SILIKON 1000 contains no preservatives or other ingredients.

INDICATIONS FOR USE

SILIKON 1000 is indicated for use as a prolonged retinal tamponade in selected cases of complicated retinal detachments where other interventions are not appropriate for patient management. Complicated retinal detachments or recurrent retinal detachments occur most commonly in eyes with proliferative vitreoretinopathy (PVR), proliferative diabetic retinopathy (PDR), cytomegalovirus (CMV) retinitis, giant tears, and following perforating injuries. SILIKON 1000 is also indicated for primary use in detachments due to Acquired Immune Deficiency Syndrome (AIDS) related CMV retinitis and other viral infections affecting the retina.

CONTRAINDICATIONS

- SILIKON 1000 is contraindicated in patients with known hypersensitivity to silicone oil.
- In pseudophakic patients with silicone intraocular lenses.

WARNINGS

- Oil-induced pupillary block and angle closure can occur in aphakic eyes if a six o'clock iridectomy is not performed.

PRECAUTIONS

- Do not use a vial for more than one patient.
- Discard unused portion.
- Do not admix with any other substances prior to injection.
- Do not resterilize.
- Discard following expiration dating.
- An underfill may result in an ineffective inferior tamponade and an overfill may result in corneal abnormalities and elevated IOP.
- The use of SILIKON 1000 as a long term tamponade has not been studied and must be determined by the treating physician. SILIKON 1000 should be removed when, in the judgment of the physician, the retinal attachment would not be comprised.

ADVERSE REACTIONS

The safety profile of SILIKON 1000 has been evaluated in a multicenter US based clinical trial (757 CMV eyes and 1,816 non-CMV eyes).

The following adverse reactions were observed during the clinical trials with SILIKON 1000.

Table 1 - 6 Months and Last Examination for Safety Outcomes

OUTCOME	VISIT[1]	CMV	Non-CMV
Emulsification in eyes w/oil	6 month Last visit	1% 1%	3% 3%
Cataract in phakic eyes	6 month Last visit	64% 38%	63% 71%
Hypotony*	6 month[2] Last visit	6% 4%	19% 19%
Elevated IOP	6 month[3] Last visit	0% 1%	3% 5%
Corneal opacity/abrasion*	6 month[4] Last visit	6% 4%	26% 31%

* The rate of previous vitreoretinal operative procedures was 14% for CMV patients and 86% for non-CMV patients.

[1]The last visit may have occurred anytime post-operatively, and the 6 month visit may have occurred post-operatively between 137 and 272 days

[2]Incidence rate of hypotony in non-CMV subjects at 6-months postoperatively was significantly greater in aphakic (21%) and pseudophakic (17%) eyes versus phakic (7%) eyes ($p < 0.01$).

[3]Incidence rate of elevated IOP in non-CMV subjects at 6-months postoperatively was significantly greater in phakic eyes (7%) versus aphakic (3%) and pseudophakic (2%) eyes ($p = 0.03$).

[4]Incidence rate of corneal opacity/abrasion in non-CMV subjects at 6-months postoperatively was significantly greater in aphakic (30%) and pseudophakic (21%) eyes versus phakic (8%) eyes ($p < 0.01$). Incidence rate of corneal opacity/abrasion in CMV subjects at 6-months postoperatively was significantly greater in aphakic (20%) and pseudophakic (11%) eyes versus phakic (4%) eyes ($p = 0.04$).

Table 2 - Safety Results at 6, 12, and 24 Months
Stratified by Complete Attachment and Macula Attachment

	CMV Eyes		Non-CMV Eyes		
Outcome	**6 mos.**	**12 mos.**	**6 mos.**	**12 mos.**	**24 mos.**
Emulsification in eyes with oil remaining					
with complete attachment	1%	2%	3%	2%	6%
with macula attachment	1%	2%	2%	3%	5%
Cataract in phakic eyes					
with complete attachment	64%	81%	64%	73%	89%
with macula attachment	63%	82%	63%	74%	80%
Hypotony					
with complete attachment	5%	4%	16%	14%	10%
with macula attachment	5%	5%	16%	16%	11%
Elevated IOP					
with complete attachment	0%	2%	3%	4%	5%
with macula attachment	0%	2%	3%	4%	5%
Corneal Opacity/abrasion					
with complete attachment	5%	5%	23%	23%	31%
with macula attachment	5%	4%	23%	25%	34%

CLINICAL STUDIES

The safety and effectiveness of SILIKON 1000 has been demonstrated in a United States multicenter clinical trial involving 2754 eyes. The Core study analysis included 2573 eyes ~~and~~ in 2439 patients, consisting of 757 CMV eyes and 1816 non-CMV eyes (935 PVR, 359 PDR, 291 trauma, and 231 giant tears). An additional 181 eyes were treated with SILIKON 1000 for diagnoses other than those detailed above which were not represented in the Core Study analysis. The effectiveness of SILIKON 1000 was measured by anatomical (macula attachment and complete retinal attachment) and visual acuity (ambulatory and preservation), see Table 3.

Table 3

SUMMARY OF EFFECTIVENESS OUTCOMES
OF SILIKON 1000 IN CMV AND NON-CMV EYES

Effectiveness Parameters - %	CMV		Non CMV	
	6 months	Last Visit	6 months	Last Visit
Macula Attachment	94	94	89	87
Complete Attachment	77	80	70	69
Preserved Vision	45	51	84	79
Ambulatory Vision	66	63	38	33

DIRECTIONS FOR USE

SILIKON 1000 can be used in conjunction with or following standard retinal surgical procedures including scleral buckle surgery, vitrectomy, membrane peeling, and retinotomy or relaxing retinectomy.

SILIKON 1000 should be injected in the posterior chamber only, and should be filled to the iris plane. An underfill may result in an ineffective inferior tamponade. An overfill may result in complications such as corneal abnormalities and elevated IOP. Air bubbles should be absent from the SILIKON 1000 in the syringe prior to instillation. SILIKON 1000 is supplied in 10 mL glass vials with 8.5ml of sterile silicone oil, which is adequate for an average eye, but highly myopic eyes may require a larger volume.

The patient should be monitored closely by the physician for development of glaucoma, cataract, and corneal complications and be scheduled for follow-up reexamination at regular intervals.

As there is a possible correlation between the migration of SILIKON 1000 into the anterior chamber and the appearance of corneal changes such as edema, hazing or opacification, Descemet's folds, or decompensation, regular monitoring of the patient's corneal status should be performed and early corrective action taken if necessary, including extraction of the oil from the anterior chamber. Large bubbles or droplets of oil in the anterior chamber can be removed manually by syringe. Further standard practice for medical treatment of the keratopathy is recommended

Temporary pressure increases occurring several weeks after surgery which either normalize spontaneously or can be corrected by surgical treatment are those in which the SILIKON 1000 may cause a mechanical blockage of the pupil or inferior iridectomy or causes chamber angle closure by forcing its way anteriorly. In these situations some of the oil may be withdrawn to relieve the mechanical force of the oil interface. Presence of droplets in the anterior chamber may also cause a chronic outflow obstruction of the trabecular meshwork. In such situations, elevated intraocular pressure can be managed with anti-glaucoma medication in the majority of patients with outflow obstructions.

ASSEMBLY INSTRUCTIONS

Caution: The outer surface of the SILIKON 1000 vial is not sterile and the vial should not be introduced into the sterile field.

The injection may be through a sclerotomy via cannula attached directly to a syringe or through a scleral sutured cannula.

Sterile Transfer

1. Outside the sterile field, remove the SILIKON 1000 vial from the clear polyethylene bag and place it in a stable location. DO NOT SHAKE SILIKON 1000.

2. Hold the SILIKON 1000 vial firmly, and remove the aluminum seal and stopper.

3. Within the sterile field, securely place a 20 gauge cannula on a 10 ml syringe.

4. Hold the vial within reach of the sterile field and aspectically introduce the cannula fitted to the syringe into the vial and withdraw the SILIKON 1000 taking care not to introduce air bubbles. Two persons are required for this procedure.

5. After the SILIKON 1000 has been completely transferred to the syringe, remove the 20 gauge cannula from the syringe and dispose of it properly. Securely place a new sterile cannula onto the syringe.

6. The SILIKON 1000 is now ready to be used. The syringe may be stored temporarily with the cannula pointed upward to allow any air bubbles to come to the tip for easy removal.

7. At the conclusion of the procedure properly discard the syringe and any remaining SILIKON 1000.

All components for Single Use Only

Do Not Resterilize

The Use of SILIKON 1000

Properties

SILIKON 1000, by virtue of its high surface tension, functions as a postoperative retinal tamponade, providing a stabilizing retention force on the reattached retina. The high surface tension allows SILIKON 1000 to seal retinal breaks and prevent slippage and folding of retinal tears by exerting a counteractive force against the reattached retina.

SILIKON 1000 has a lower viscosity which facilitates manual intraocular instillation and removal using a hand-held syringe. Lower viscosity reduces instillation and removal time in which intraocular pressure must be controlled.

SILIKON 1000 has a refractive index similar to aqueous. It is optically clear and does not interfere with visualization of the retina.

Toxicity

In a series of *in vitro* and *in vivo* tests, SILIKON 1000 has been shown to be non-toxic, non-pyrogenic, non-mutagenic, and non-irritating.

General Use

Before SILIKON 1000 is injected, tissue debris, blood and intraoperative aids such as perflourocarbon liquids should be completely removed.

SILIKON 1000 may be injected into the vitreous cavity transconjunctivally and transclerally following vitrectomy. SILIKON 1000 is normally injected under pressures which depend on the diameter of the injection cannula. During the injection, care should be taken to maintain reasonable intraocular pressure. The oil can be injected into the vitreous from the syringe via a single-use cannulated infusion line or syringe needle. Use of an automated injection system, will assist the physician in avoiding an underfill or overfill condition. Subretinal fluid can be drained with a flute needle concurrent with SILIKON 1000 injection.

The vitreous space can be filled with the oil to between 80% and 100% while exchanging for fluid, perfluorocarbon liquid, or air, taking necessary precautions to avoid high intraocular pressure from developing during the exchange. Because SILIKON 1000 is less dense than the eye's aqueous humor, a basal iridectomy at the 6 o'clock meridian (Ando iridectomy) is recommended to minimize oil induced pupillary block and early angle-closure glaucoma. At the physician's discretion, it may be desirable to have the patient assume a face-down posture during the first 24 hours following surgery.

When a perfluorocarbon is used intraoperatively, small droplets of perfluorocarbon may become mixed with SILIKON 1000 and may be difficult to distinguish from air bubbles. However, within seconds, the air bubbles will float anteriorly in SILIKON 1000, while the small perfluorocarbon droplets will descend onto the surface of the retina, making them easier to identify and aspirate.

It is recommended that SILIKON 1000 be removed at an appropriate interval within 1 year following instillation if the retina is stable, attached, and without significant remnants of proliferation. Although there is insufficient clinical evidence to support justification for longer

term tamponade, whether or not the oil should be removed in patients at high risk for redetachment or the development of phthisis and shrinkage due to hypotony must be determined individually by the physician. In order to minimize the number of invasive traumatic experiences for patients with AIDS and CMV retinitis at high risk for redetachment and who have a shortened expected lifespan, it may be desirable to avoid silicone oil removal procedures if the patient concurs.

SILIKON 1000 can be removed from the posterior segment by withdrawal with a normal 10 mL syringe and a wide bore 1 mm cannula. By repeated oil-fluid exchange most of the remaining small silicone oil droplets can subsequently be mobilized and removed from the eye. Alternatively, oil may be passively removed by infusion of an appropriate aqueous solution under the oil bubble, while allowing the oil to effuse out of a sclerotomy incision, or through a limbal incision in aphakic patients.

HOW SUPPLIED

SILIKON 1000 is supplied in 10mL glass vials filled with 8.5 mL of sterile silicone oil.

STORAGE

SILIKON 1000 should be stored at room temperature at 59 degrees F - 89 degrees F (15°C to 32°C).

For intraocular use only.

Manufactured by: Richard-James, Inc.
2 Centennial Drive
Peabody, MA 01960
(508) 532-0666

Supplied by: Richard-James, Inc.
For: Alcon Laboratories
6201 South Freeway
Fort Worth, TX 76134
(800) 862-5266

REFERENCES

CMV

Davis JL, MS, Lai M-Y, Trask DK, Azen SP. *Silicone Oil in Repair of Retinal Detachments Caused by Necrotizing Retinitis in HIV Infection.* Arch. Ophthalmol. 113:1401-1409 (1995).

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